REMARKS

General:

Claims 1-11 remain pending in the application. Claims 1-11 stand rejected.

Claim 1 has been amended to provide a formal antecedent for the term "the powder diffraction pattern" at original page 19, line 5, and to comply with 37 CFR § 1.75(i). The amendment to claim 1 raises no new issues, and puts the claim in better order for allowance or appeal, by removing formal defects. The amendment is therefore believed to be proper after final rejection. No new matter has been added by this amendment, and no change has been made to the scope of the claim.

Applicants' attorneys apologize for any inconvenience caused by the inadvertent omission of the 1999 paper from the previous response. A copy is filed herewith.

Abstract:

As requested by the examiner, a shortened abstract is filed herewith.

35 USC § 112, first paragraph:

Claims 1-11 are rejected as containing subject matter not described in such a way as to enable one skilled in the art to use the invention. Although the examiner's theory is nowhere explicitly stated, Applicants assume from the lengthy citation to *In re Wands* that the examiner considers that putting the invention into effect on the basis of the present disclosure would require undue experimentation.

However, the examiner goes on to remark that "[t]he Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable." The relevance of this remark is not understood. The present invention has only an incidental connection to molecular biology (simply because some of the molecules to which it is applied may be of biological origin), and no connection whatever to genetic engineering. The "genetic algorithm" referred to at page 10, line 12 is a mathematical technique used for the iterative solution of problems not amenable to analytic solution, and the comparison between the computable variables and actual mutating genes at

page 10, lines 11-18 is metaphorical and only illustrative. It is clearly not to be read literally, and those skilled in the art would understand that.

This raises the question of relevant art. The applicants do not understand why this application was assigned to an examiner in Group Art Unit 1631. Group Art Unit 1631 is captioned "Bioinformatics," and is indented under Group 1630: Recombinant Molecular and Micro-Biology, Multicellular Organisms, within Patent Technology Center 1600: Biotechnology and Organic Chemistry. Bioinformatics appears to consist essentially of handling the data content of gene and protein sequences.

However, the invention in the present application relates to the application to crystallography of a method of mathematical simulation using algorithmic computation, and would be more correctly classed in Class 703/2, Modeling by mathematical expression, or Class 703/12, Simulating nonelectrical device or system – Chemical.

In this connection, it is noted that the only patent reference cited in the present application is classified solely within Class 378, X-ray or gamma ray systems or devices, and primarily in subclass 73, Specific application: Diffraction, reflection, or scattering analysis: Diffractometry: Crystalography. This factor "is generally controlling over all else" under MPEP § 903.08(e)(E). It is noted that the present application was classed by the International Searching Authority to the very similar Class G10N 23/20, Physics – Measuring - Investigating or analysing materials by determining their chemical or physical properties - By the use of wave or particle radiation e.g. X-rays, neutrons - By using diffraction of the radiation, e.g. for investigating crystal structure or by using reflection of the radiation. It is noted that the present application was initially assigned by the U.S. Patent Office to Group Art Unit 2876, apparently implying that it was seen as some sort of calculating machine.

In view of the foregoing, it is respectfully requested that the application be reviewed by a supervisory patent examiner under MPEP § 903.08(d) to determine whether transfer to a different technology center is desirable. (Transfer by the primary examiner as "best examinable" under 903.08(d) appears to be unavailable, because it would require classification into the present art unit to be proper.)

If the examiner's position is that undue experimentation would be required to carry out the invention, that position is untenable. "The fact that experimentation may be complex

does not make it undue, if the art typically engages in such experimentation." MPEP § 2164.01, citing to *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The relevant art for this purpose is the art of determining crystal structures. Specifically, it is the art of determining crystal structures that remain difficult to analyze, because all the easy ones were determined years ago. This is an art in which very large amounts of trial and error are normal, because the only way to determine many of these structures is to try guess after guess until a workable solution is found. That is why people devote the time and trouble to develop inventions like the present one: it makes the process of trial and error quicker and easier, because the computer does much of the tedious work.

From page 3, line 19 to page 4, line 22, the examiner argues that he cannot determine the probability of success on any given attempt. Although true, that does not assist the examiner. The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The mere absence of evidence of operability beyond the disclosed embodiments is not sufficient to support the examiner's case. *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974).

The examiner's argument is confused by the examiner's reference to the predetermined threshold first recited in claim 1 at page 19, lines 17-18. The threshold is not used to guard against divergent processes. See page 19, lines 18-29. It is used to stop the process when it succeeds. As long as all survivors have a fitness higher than the threshold, the process continues (lines 18-22). If any survivor has a fitness less than the threshold, it is accepted as a success (lines 26-29). Thus, it is implicit that a low fitness is good, and the starting values have a fitness higher (worse) than the threshold.

If a particular iteration fails to find a structure with a fitness value below the threshold, then the researcher merely starts again with different initial values, or with different rules for altering the values of the variables between iterations. That requires experimentation, but it does not require undue experimentation.

From page 4, line 22 to page 5, line 4, Examiner Marschel reasserts Examiner Hartter's contention that the "predetermined thresbold is not defined in the specification so as to enable the reader to reproduce it." That erroneously assumes the threshold has a specific value. The predetermined threshold may be any number. As shown above, it is implicitly a number less than the fitness values of the initial population. The examiners have shown no reason why a person skilled in the art cannot simply pick a reasonable number within the available range. The examiners' attempt to reverse the burden of proof, and require the applicants to provide detailed instructions for every conceivable, and inconceivable, molecule that may be crystallized in the next twenty years is incorrect as a matter of law, and unrealistic as a matter of fact.

From page 5, line 7 to page 8, line 6, the examiner argues that the specification does not enable the generalization from the specific equation recited in claim 5 to the general scope of claim 1. The examiner's argument appears to be based on the premise that "the results of experiments in genetic engineering are unpredictable" (page 6, lines 4-5). As pointed out above, the present invention has no connection with genetic engineering. The proper field of art for assessing the generalization of the equation is the art of mathematical statistics, which is an extremely predictable art.

At page 6, lines 8-22, the examiner asks the applicant to provide documentation to show that the fitness calculations are within the general knowledge of the person skilled in the art. The examiner is clearly expected to be familiar with the general knowledge in the art that he is examining (See for example MPEP § 2144.03, and § 2164.04, second sentence.) so these documents should not be required merely to instruct the examiner. The examiner does not assert that these matters are not within the general knowledge, so these documents are not required to refute the examiner's case. As noted above, the mere absence of evidence in the record is not sufficient to support a rejection. The examiner must give actual reasons for questioning the sufficiency of the enablement. There thus seems to be no proper basis for imposing on the applicants the burden of proof of the general knowledge.

However, in the interests of a prompt resolution of this matter, some samples both of teaching materials and of research papers are filed herewith to show the state of the art in the field of fitness values. For practical reasons, most of these materials were collected from the

internet, and do not have dates of original publication. See also steps 68 and 74 in Fig. 6 of Wormington.

The examiner's attention is drawn in particular to the work by Peter Stephens at SUNY Stony Brook on the Powder Structure Solution Program. The fitness formula used in PSSP is understood to be an example of a later-derived equivalent to the formula recited in claim 5, showing that it is within the ability of those skilled in the art to derive such alternatives.

At page 6, line 24 to page 7, line 4, the examiner asks how the simultaneous fitting of both X-ray and neutron diffraction data produces a fitness. The purpose of the examiner's question is not understood. The object of the invention is to produce a final trial structure identical, or very nearly identical, to the actual structure of the real crystal. The "fitness" of a trial structure is simply a measure of how similar it is to the real crystal. It is believed to be self-evident that comparing real experimental data on the real crystal, such as X-ray diffraction data or neutron diffraction data, with calculated experimental data on the trial structure is likely to provide a useful indication of how similar the two structures are, that is to say, a useful input to an assessment of fitness. It is believed to be self-evident that comparing several different sets of data simultaneously, for example, both X-ray and neutron diffraction data, is likely to afford a better indication of fitness than any one set of data alone.

At page 7, lines 4-6, the examiner asserts that "the trial structures are expected to be in silico, and thus unavailable for any diffraction data determination." The trial structures are mathematically simulated structures. The diffraction data determined for the trial structures at page 11, lines 3-4 of the application, are of course calculated diffraction data. Methods of calculating the diffraction data for a given structure are known. See, for example, the references cited by Wormington et al. at col. 5, lines 51-62. The calculation is not affected by being based on a simulated structure rather than a measured one. The purpose of the examiner's remark is not understood.

At page 7, lines 6-9, the examiner says that he does not understand what fitness is determinable by evaluating packing. Packing is a property of the crystal that is easily measured for the real crystal, is easily calculated for the trial structure, and will be affected by errors in the trial structure. It is therefore a proper datum to use in assessing the similarity

of the real crystal and the trial structure, that is to say, the fitness. The examiner's difficulty is not understood.

With reference to the notation in the chi-squared equation, attached for the examiner's convenience are two pages from a structure factor tutorial (available on the internet, starting at http://www.yorvic.york.ac.uk/~cowtan/sfapplet/sfintro.html). One of the attached pages explains the inversion from conventional x, y, z spatial co-ordinates to reciprocal h, k, l co-ordinates (Miller indices). The other explains why the structure factor magnitude $|F(h)|$ is commonly used as a starting point. The tutor switches without explanation from F(h,k) in section 4 of the tutorial to F(h) in section 6. The use of functions with reduced numbers of arguments is evidently so well understood in the art as to require no explanation even in a tutorial. However, the examiner's concern about the apparent discrepancy between the arguments for the terms used in the chi-squared equation and the terms defined at claim 5, lines 6-9 and page 11, lines 11-14 is believed to be due to a misreading of the text. A comma makes all the difference. When the author requires a two-dimensional argument, he writes a double subscript as V_{hk}, without punctuation. When he writes $F_{h,k}$ with a comma, it is merely a shorthand for F_h, F_k.

The scale factor c is a necessary consequence of the need to subtract a structure factor from an intensity. It gets rid of irrelevant extrinsic variables, and allows the dimensions of F^2 and I to be reconciled. Some web pages on the subject are attached: the examiner will see that one of them is from a university lecturer's course notes, last updated in 1997. Tickle and Driessen demonstrates why the scale factor cannot usefully be discussed in more detail in a document such as the present application. The attached extract is concerned almost entirely with scale factor corrections due to the structure and composition of the specific molecule.

The examiner twice lists the eight factors identified in *In re Wands* as "factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not support the enablement requirement." Those factors are:

(A) The breadth of the claims.

(B) The nature of the invention.

(C) The state of the prior art.

(D) The level of one of ordinary skill.

(E) The level of predictability in the art.

(F) The amount of direction provided by the inventor.

(G) The existence of working examples.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The examiner does not discuss factors (A) and (B) at all.

The examiner's only contribution to factor (C) is to require the applicants to document that certain matters are common general knowledge. The examiner never takes a position as to whether the matters are in fact known or not.

The examiner's position on factors (D) and (E) does not advance the inquiry, because the examiner relies on findings of skill and predictability in a different and unrelated art.

As to factor (F), the examiner's criticisms of the direction provided by the applicants are believed to be unfounded for the reasons set out above.

As to factor (G), the examiner does not dispute that working examples, and not merely prophetic examples, are provided.

As to factor (H), the examiner's position appears to be that he does not know how much experimentation is needed.

In re Wands allows for other factors to be considered, but the examiner does not clearly raise any.

Thus, of the eight *Wands* factors, it is submitted that the examiner has taken erroneous positions on three, equivocal positions on two, and no position on the remaining three. It is therefore submitted that the balancing test required by *Wands* must conclude that the examiner has not made out a prima facie case of lack of enablement. It is further submitted that, in view of the high level of skill in the art of mathematical statistics and the high level of patience in the art of crystallography, the specification does sufficiently enable the invention as claimed, and does not require an undue level of experimentation.

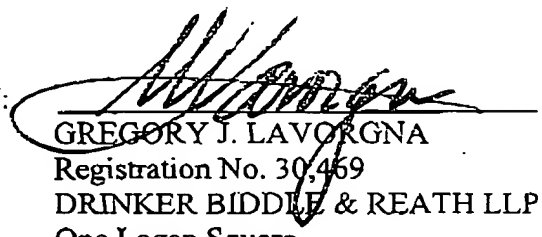
Conclusion:

For all of the above reasons, it is believed that claims 1-11 comply with the requirements of 35 U.S.C. § 112, and the examiner's other requirements have been met.

Reconsideration of the examiner's objections and rejections and an early notice of allowance of all claims are earnestly solicited.

Respectfully submitted,

WILLIAM IAN DAVID et al.

BY: 

GREGORY J. LAVORGNA
Registration No. 30,469
DRINKER BIDDLE & REATH LLP
One Logan Square
18th & Cherry Streets
Philadelphia, PA 19103-6996
Tel: 215-988-3309
Fax: 215-988-2757
Attorney for Applicants

Application No. 09/463,881
Filing Date April 18, 2001

MARKED UP COPIES OF AMENDED TEXT

In the abstract:

A[n improved] method and apparatus for determining molecular crystal structures [is provided which] enables molecular crystal structures to be identified using only powder diffraction data[, that is considerably faster than conventional crystal modeling techniques]. [With the improved crystal modeling method and apparatus] T[t]rial [molecular] crystal structures are reduced to a [unique] set of variables [based on co-ordinates] representative of the location and orientation of the molecule, [and where appropriate at least one co-ordinate representative of a] torsion angles, bond lengths or bond angles. The [In addition, the total quantity of] experimental [powder] diffraction data [is reduced to] provides a reduced representation of the [diffraction] data in the form of a structure factor intensity listing and covariance matrix. Trial [crystal] structures are postulated and each is defined using the set of variables, which [that] are used in determining a fitness of each trial structure with respect to the reduced representation of the experimental data. A [trial] crystal structure is output [as an accurate representation of the actual crystal structure,] when the fitness value for the trial structure is less than or equal to a predetermined threshold [value]. [With the improved crystal modeling method and apparatus,] I[i]dentification of complex molecular crystal structures can be performed in seconds or minutes using [the current generation of] conventional personal computers or workstations [as opposed to the hours and often days required with conventional techniques].

In the claims:

1. (amended) A method for determining molecular crystal structures from powder diffraction data comprising the steps of:

providing a powder diffraction pattern of a molecular crystal structure;

generating a reduced representation of the powder diffraction pattern in dependence on a predetermined unit cell and space group of the molecule under examination in which the total quantity of diffraction data is significantly reduced whilst maintaining the

characteristics of the diffraction data that are representative of the crystal structure under examination;

determining a set of variables for describing trial molecular structures, derived from predetermined internal coordinates and said space group;

assigning values to said variables thereby creating a population of trial structures each defined by a unique set of values for said variables;

calculating a fitness for each trial structure with respect to the reduced representation of the powder diffraction pattern;

determining whether any one of the calculated fitnesses is less than or equal to a predetermined threshold;

where none of the calculated fitnesses is less than or equal to the threshold value, selecting at least one survivor from the population of trial structures, altering the values of the variables of at least one of the survivors in accordance with one or more predetermined rules, calculating the fitnesses of the new trial structures; and repeating the steps of selecting survivors, altering the values of the variables and calculating the fitnesses of the new trial structures until at least one of the calculated fitnesses is less than or equal to the threshold value, and

where at least one of the calculated fitnesses is less than or equal to the threshold, outputting at least on trial molecular crystal structure represented by the successful sets of values.